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# Psychological Medicine

## Neural responses to fearful eyes in children with conduct problems and varying levels of callous-unemotional traits --Manuscript Draft--

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Abstract:	<p>Background: Children with conduct problems are a heterogeneous group. Those with high levels of callous-unemotional traits (CP/CU+) appear emotionally under-reactive at behavioural and neural levels, while those with low levels of CU traits (CP/CU-) appear emotionally over-reactive, compared with typically developing (TD) Controls. Investigating the degree to which these patterns of emotional reactivity are malleable may have important translational implications. Instructing participants with CP/CU+ to focus on the eyes of fearful faces (i.e. the most salient feature) can ameliorate their fear recognition deficits, but it is unknown whether this is mediated by amygdala response. It is also unknown whether focusing on fearful eyes is associated with increased amygdala reactivity in CP/CU-.</p> <p>Methods: fMRI was used to measure neural responses to fearful and calm faces in children with CP/CU+, CP/CU- and TD Controls (n=17 per group). On half of trials participants looked for a blue dot anywhere within target faces; on the other half, participants were directed to focus on the eye region.</p> <p>Results: Reaction time (RT) data showed that CP/CU- were selectively slowed in the fear/eyes condition. For the same condition, CP/CU- also showed increased amygdala and subgenual ACC/OFC responses compared with TD Controls. RT and amygdala response to fear/eyes were correlated in CP/CU- only. No effects of focusing on the eye region were observed in CP/CU+.</p> <p>Conclusions: These data extend the evidence base suggesting that CU traits index meaningful heterogeneity in conduct problems. Focusing on regulating reactive emotional responses may be a fruitful strategy for children with CP/CU-.</p>

## **Neural responses to fearful eyes in children with conduct problems and varying levels of callous-unemotional traits**

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## **Abstract**

**Background:** Children with conduct problems are a heterogeneous group. Those with high levels of callous-unemotional traits (CP/CU+) appear emotionally under-reactive at behavioural and neural levels, while those with low levels of CU traits (CP/CU-) appear emotionally over-reactive, compared with typically developing (TD) Controls. Investigating the degree to which these patterns of emotional reactivity are malleable may have important translational implications. Instructing participants with CP/CU+ to focus on the eyes of fearful faces (i.e. the most salient feature) can ameliorate their fear recognition deficits, but it is unknown whether this is mediated by amygdala response. It is also unknown whether focusing on fearful eyes is associated with increased amygdala reactivity in CP/CU-.

**Methods:** fMRI was used to measure neural responses to fearful and calm faces in children with CP/CU+, CP/CU- and TD Controls (n=17 per group). On half of trials participants looked for a blue dot anywhere within target faces; on the other half, participants were directed to focus on the eye region.

**Results:** Reaction time (RT) data showed that CP/CU- were selectively slowed in the fear/eyes condition. For the same condition, CP/CU- also showed increased amygdala and subgenual ACC/OFC responses compared with TD Controls. RT and amygdala response to fear/eyes were correlated in CP/CU- only. No effects of focusing on the eye region were observed in CP/CU+.

**Conclusions:** These data extend the evidence base suggesting that CU traits index meaningful heterogeneity in conduct problems. Focusing on regulating reactive emotional responses may be a fruitful strategy for children with CP/CU-.

## Introduction

Conduct disorder (CD) and conduct problems (CP) refer to a persistent pattern of antisocial behaviour in young people, and represent a significant public health cost (Romeo et al., 2006). Children with conduct problems are a heterogeneous group. Levels of callous-unemotional (CU) traits, i.e. a lack of guilt and empathy, have been shown to differentiate individuals with conduct problems in terms of aetiology, behaviour, and neurocognitive processing (see Frick & Viding, 2009, for a review).

Research suggests that affective processing styles differ between children with conduct problems and low levels of CU traits (CP/CU-) and those with high levels of CU traits (CP/CU+). Behavioural data indicate that children with CP/CU+ show a *hypo*-reactive response profile to affective cues (Loney et al., 2003; Sharp et al., 2006) coupled with difficulties in processing and recognising others' fearful and sad facial and vocal expressions (Blair et al., 2001; Blair et al., 2005). In contrast, CP/CU- children may show an exaggerated or *hyper*-reactive response profile to emotional stimuli, and a hostile attribution bias, where even neutral stimuli are construed as threatening (Frick et al., 2003a; Dadds et al., 2006). This emotional reactivity is often coupled with poor emotion regulation skills (Frick & Morris, 2004), which can result in reactive and unplanned aggression. Indeed, aggression in this subgroup is usually reactive in nature (Frick et al., 2003b), while aggressive behaviour in CP/CU+ children may either be reactive or proactive, i.e. used in pursuit of a goal (Frick & Viding, 2009).

Neuroimaging data have also shown neurocognitive differences in affective processing between CP/CU subtypes. Studies contrasting CP/CU+ against typically developing (TD) controls have found evidence for reduced amygdala response to others' fearful facial expressions (Marsh et al., 2008; Jones et al., 2009), mirroring behavioural evidence of emotional hypo-reactivity in this group. Similarly, one recent study from our group directly contrasting CP/CU+ and CP/CU- found a significantly greater amygdala response to fearful faces presented below the level of conscious awareness in children with CP/CU- compared with CP/CU+ (Viding et al., 2012).

However, findings from studies investigating conduct problems independent of CU present a mixed picture, with some reporting reduced amygdala responses to negative facial expressions (Passamonti et al., 2010) and negatively valenced pictures (Sterzer et al., 2005) relative to TD controls, while others report increased amygdala response in children with CP using similar stimuli (Herpertz et al. 2008). One explanation for these apparently conflicting findings was suggested by a recent study (Sebastian et al., 2012), which found that amygdala response to negatively valenced cartoon stimuli in CP children was positively associated with CP symptoms after controlling for CU traits, and negatively associated with CU traits after controlling for CP symptoms. Patterns of opposing influences on amygdala reactivity may thus exist within the same CP sample.

Behavioural and neuroimaging data have converged on fear processing as an important source of difference between CP/CU-, CP/CU+ and TD controls (Marsh et al., 2011). However, the cognitive mechanisms underpinning these differences remain a subject of debate. Facial fear is unique in that it is identified almost entirely by eye region information (Adolphs et al., 2005). One study of fear processing in a community sample of adolescent males found that a deficit in recognising fearful expressions in participants with high levels of CU traits could be temporarily ameliorated by instructing them to attend to the eye region of the face (Dadds et al., 2006). A follow-up study using eye-tracking (Dadds et al., 2008) found that adolescents with high levels of CU made fewer and shorter fixations to the eye region of fearful faces under free viewing conditions than those with low levels of CU traits. It is therefore possible that reduced amygdala response to fear in CU+ children (Marsh et al., 2008; Jones et al., 2009) is secondary to reduced attention to the eyes (Moul et al., 2012). A key aim of the current study was to investigate whether directing CP/CU+ children to attend to the eye region of a fearful face would normalise their amygdala response.

A second important aim was to investigate the effects of directing attention to the eye region in children with CP/CU-. While there is evidence to suggest increased emotional reactivity to emotional stimuli in this group (e.g. Frick et al., 2003a, 2003b), few neuroimaging studies have explored the mechanisms underlying this reactivity, or how the degree of reactivity may be modulated. For

example, directing attention to the eyes might have no effect on amygdala response. Equally, however, attending to eyes may serve to augment amygdala response relative to the degree of activation observed when attending to the whole face. Similarly, the effects of affective arousal on cognitive task performance have not yet been explored in relation to different CP/CU subtypes. In the current study we investigated whether instruction to focus on the eye region during fear processing interfered with performance of a concurrent task, predicting that this effect would be greater in the CP/CU- group relative to TD controls and children with CP/CU+.

We devised a task in which participants judged whether a blue dot was present or absent from target faces which were either fearful or calm. In half of blocks of each valence (fear vs. calm), the dot was presented anywhere within the face (meaning that the whole face, including the eyes, needed to be scanned); while in the other half the dot was presented in the eye region only. Participants were directed to attend to either the whole face or the eye region accordingly. Our rationale for using the dot task was two-fold: first, accurate performance ensured that participants were focusing on the instructed region of the face; second, it introduced an implicit emotion regulation component, in which successful task performance depends on automatically regulating responses to distracting affective information (fearful faces) (Ochsner & Gross, 2005). This allowed us to test two hypotheses. First, we hypothesised that CP/CU+ would activate the amygdala to a greater extent to fearful faces when instructed to focus on the eye region compared with the whole face. Second, given evidence of emotion regulation deficits in CP/CU-, we predicted that this group would show a relatively greater amygdala response to fearful faces when instructed to focus on the eye region compared with other conditions and experimental groups; and that this would be accompanied by a selective reduction in task performance, representing a reduced ability to implicitly regulate emotion in pursuit of a goal.

## Methods

*Participants:* Participants largely overlapped with a sample reported previously (Sebastian et al., 2012; Viding et al., 2012). Full details of sample recruitment are reported in these studies and in the supplementary material. Participant characteristics are displayed in Table 1. The study was approved by the University College London Research Ethics Committee (Project ID number: 0622/001).

Fifty-five males aged 10-16 were scanned: 38 with a research diagnosis of current conduct problems (CP) based on combined parent- and teacher- report on the Child and Adolescent Symptom Inventory (CASI-4R; Gadow & Sprafkin, 2009) Conduct Disorder subscale (CASI-CD); and 17 age-, IQ-, handedness- and SES-matched typically developing (TD) controls. Data from four children with CP were excluded due to: excessive motion and poor task accuracy (1 CP); motion plus suspected autism spectrum and tic disorder (1 CP); scanner refusal (1 CP) and technical problems (1 CP). The 34 remaining participants with CP were assigned to low vs. high callous-unemotional trait groups (CP/CU- vs. CP/CU+, n=17 per group) on the basis of a median split on combined parent- and teacher- reported scores on the Inventory of Callous-Unemotional Traits (ICU; Essau et al., 2006). Median ICU score within the CP group was 44.5: all TD Controls scored below this CP group median.

For all groups, exclusion criteria included a previous diagnosis of any neurological or psychotic disorder, or a current prescription for psychiatric medication. (We later found that three participants (2 CP/CU-, 1 CP/CU+) had been medicated for ADHD symptoms during scanning. However, analyses conducted with and without these participants were very similar, and so their data were retained in reported analyses). To recruit a representative sample of children with conduct problems, common co-morbidities (attention deficit hyperactivity disorder (ADHD), generalised anxiety disorder (GAD), major depressive disorder (MDE) and substance/alcohol abuse) were not used as exclusion criteria, but current parent-reported symptom counts were obtained using the CASI-4R.

\*\*\*\*\*Table 1\*\*\*\*\*



*Experimental Task:* Stimuli comprised fearful and calm faces of four individuals taken from the NimStim (two male, two female, with mouths closed). Image size was standardised, and all faces were presented in greyscale with the hair cropped. Stimuli were presented on a white background. Four block types were presented using a 2x2 factorial design with factors Emotion (fear, calm) and Region (eye region, whole face). Sixteen blocks were presented in four sets of four blocks containing one of each condition: fear/eyes, calm/eyes, fear/face, calm/face. Block order was randomised within each set of four blocks.

Participants indicated with a keypress response on every trial whether there was a blue dot present on the face or not. In the 'eyes' blocks, half the stimuli had a dot present within the eye region of the face (but not covering the eye), while for the other half there was no dot present. In 'face' blocks, the blue dot was located in the wider face area. The location of the dot varied and was counterbalanced across Emotion conditions. Each block lasted 30s, comprising 2.5s instructions, 20s face stimuli, and 7.5s fixation cross between blocks. The instruction screen reminded participants of the correct keypress responses. It also told participants whether to look at the eyes or the face for the coming block. Participants knew to expect that during 'eyes' blocks the blue dot would only be presented near the eye region, while during 'face' blocks it would only be presented in the wider face. The stimuli comprised 8 trials of 2500ms each (1750ms face presentation and 750ms ISI fixation cross). The 8 trials consisted of the two male and two female faces presented both with and without a dot present. On 'dot present' trials, the dot appeared concurrently with the face. Trial order within each block was pseudorandomised to prevent all stimuli of one type (i.e. dot, no-dot, male or female) being presented together. Participants practised the task outside the scanner, with calm faces of differing identities to those shown in the full experiment.

*Psychometric and questionnaire measures:* Participants completed the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) two-subtest version for group matching purposes, as well as Alcohol/Drug Use Disorder Identification Tests (AUDIT and DUDIT; Babor et al., 2001; Berman et al.,

2005). A parent or guardian also completed the CASI-4R scales for ADHD, GAD and MDE in order to ascertain symptom counts for common co-morbidities with conduct problems (Table 1).

*fMRI data acquisition:* A Siemens Avanto 1.5T MRI scanner with a 32 channel head coil was used to acquire a 5.5 min 3D T1-weighted structural scan, and 209 multislice T2\*-weighted echo planar volumes with BOLD contrast (1 run of 10 mins). The EPI sequence was designed to optimise signal detection and reduce dropout in OFC and amygdala (Weiskopf et al., 2006), and used the following acquisition parameters: 35 2mm slices acquired in an ascending trajectory with a 1mm gap, TE=50ms; TR=2975ms; slice tilt=-30° (T>C); flip angle=90°; field of view=192mm; matrix size=64x64. Fieldmaps were also acquired for use in the unwarping stage of data pre-processing.

*fMRI data analysis:* Imaging data were analysed using SPM8 ([www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)). Data pre-processing followed a standard sequence: the first five volumes were discarded; data were realigned; unwarped using a fieldmap; normalised via segmentation of the T1 scan with a voxel size of 2x2x2mm; and smoothed with an 8mm Gaussian filter. A block analysis compared neural activity in a 2x2 factorial design with regressors representing fear/eyes, calm/eyes, fear/face and calm/face conditions, with each block of 20s duration. Two additional regressors of no interest were included, modelling fixation (duration 7.5s) and instruction screens (duration 2.5s). These six regressors were modelled as boxcar functions convolved with a canonical haemodynamic response function. The six realignment parameters were modelled as effects of no interest. For 13 participants (3 TD Controls, 6 CP/CU-, 4 CP/CU+), extra regressors were included to model a small number of corrupted images resulting from excessive motion. These images (amounting to no more than 10% of each participant's data) were removed and the adjacent images interpolated in order to prevent distortion of the between-subjects mask. Data were high-pass filtered at 128s to remove low-frequency drifts.

At the first level, main effects of each factor (Emotion and Region) were calculated, as well as the interaction term (Emotion\*Region). Contrast images were entered into separate second-level analyses, where Group (TD Control, CP/CU-, CP/CU+) served as a between-subjects variable in one-

way ANOVAs with post hoc contrasts. For whole brain analyses, an initial threshold of  $p < .005$ ,  $k \geq 10$  (uncorrected) was used (Lieberman & Cunningham, 2009), with results reported as significant if they reached  $p < .05$ , FWE-corrected at the cluster level. As the amygdala was the a priori region of interest, we also conducted region of interest analyses in this region bilaterally using two 3mm radius spheres centred on anatomically defined central amygdala co-ordinates used in a previous study contrasting fearful and calm faces (Phillips et al., 2001) ( $\pm 20 -8 -16$ , after conversion from co-ordinates reported in Talairach space ( $\pm 20 -8 -13$ )). Results are reported if they survive small volume correction across the bilateral mask at  $p < .05$ , FWE-corrected.

## Results

### Behavioural Data

Mean reaction times (RTs) and percentage errors were calculated for each participant for each of the four conditions: fear/eyes, calm/eyes, fear/face, calm/face. Missed trial rates were low across the task (mean across all groups and conditions=0.98%, SD=1.94), and were excluded from mean RT and percentage error calculations.

*Reaction Times:* For RT data, a mixed-model ANOVA was conducted with within-subjects factors of Emotion (fear, calm) and Region (eyes, face); and with a between-subjects factor of Group (TD Control, CP/CU-, CP/CU+). There were no main effects of Region ( $p = .46$ ) or Group ( $p = .82$ ), but there was a marginal main effect of Emotion ( $F(1,48) = 3.25$ ,  $p = .078$ ), with marginally slower RTs across fear stimuli as a whole. There was also a significant Emotion\*Region interaction ( $F(1,48) = 5.41$ ,  $p = .024$ ). Simple effects tests showed that this was driven by significantly longer RTs to fear than to calm stimuli when participants were directed to attend to the eye region (mean RT for fear/eyes = 725ms and for calm/eyes = 707ms;  $p = .004$ ). In contrast, there was no significant difference between RTs for

fear vs. calm when participants attended to the face (fear/face=710ms, calm/face=713ms,  $p=.61$ ).

No other two-way interactions were significant.

The three-way interaction between Emotion, Region and Group was at trend level ( $F(2,48)=2.30$ ,  $p=.11$ ). Since we had an a priori hypothesis of group differences, we proceeded with planned t-tests.

These suggested that the significant Emotion\*Region interaction was only present for the CP/CU- group. RTs were significantly slower for fear/eyes than calm/eyes in this group (mean RT for fear/eyes=728ms and for calm/eyes=697ms,  $t(16)=3.22$ ,  $p=.005$ ). Mean RTs to fear/face vs. calm/face stimuli did not differ in the CP/CU- group ( $p=.25$ ), and there were no significant differences between any of the conditions in either the TD Controls or in CP/CU+ ( $ps>.09$ ) (Figure 1).

We also explored the two-way (condition\*region) interaction term within each group (fear/eyes-calm/eyes)>(fear/face-calm/face). This indexes the extent to which there is a relative slowing effect of the fear/eyes condition. Contrasting (fear/eyes-calm/eyes) with (fear/face-calm/face), there was a significant difference in the CP/CU- group ( $t(16)=2.97$ ,  $p=.009$ ), but no difference in either of the other groups ( $ps>.23$ , Figure 1).

\*\*\*\*\*Figure 1\*\*\*\*\*

*Errors:* The total error rate across group and condition was 3.17% (SD=3.65). For percentage error data, a mixed-model ANOVA was conducted with the same factors as for the RT data above. No main effects were significant (for Emotion  $p=.80$ ; for Region  $p=.78$ ; for Group,  $p=.12$ ). No interaction effects reached significance, although there was a marginal Region\*Group interaction ( $p=.11$ ) and a marginal three-way interaction between Emotion, Region and Group ( $p=.095$ ). On the basis of an a priori hypothesis for a three-way interaction, we explored further. While the CP/CU- group made significantly more errors than the TD group for the calm/eyes condition ( $p=.031$ ), no other effects were significant, and error data are not discussed further.

## fMRI Data

The key contrast of interest for the fMRI data mirrored the Emotion\*Region interaction from the behavioural data analyses ((fear/eyes>calm/eyes)>(fear/face>calm/face)). As with the RT data above, a significant interaction effect in the predicted direction would suggest a disproportionate effect of fear/eyes. For completeness, main effects of this contrast across groups, as well as main effects for Fear>Calm (and the reverse) are displayed in the Supplementary Information at a threshold of  $p<.005$  uncorrected,  $k\geq 10$ . Key hypotheses pertained to differences between groups for the Emotion\*Region interaction (three-way interaction), and these are reported below.

*Emotion\*Region\*Group interaction:* Given specific hypotheses regarding amygdala response, region of interest analyses were conducted using bilateral amygdala spheres as described in the Method. To test the first hypothesis that directing attention to the eyes would lead to increased amygdala response to fear in CP/CU+, we first looked at the Emotion\*Region interaction (fear/eyes>calm/eyes)>(fear/face>calm/face), and responses to the simple effect fear/eyes>fear/face in CP/CU+. No activations in the amygdala reached significance at  $p<.05$  FWE-SVC, or at  $p<.005$ , uncorrected,  $k\geq 10$ .

To test the second hypothesis, i.e. that focusing on fearful eyes would result in a disproportionate amygdala response in CP/CU- compared with other groups, all groups were compared for the Emotion\*Region interaction. Consistent with our hypothesis, the contrast CP/CU->TD Controls yielded a cluster of 6 voxels in the left amygdala that survived FWE correction (peak=[-18 -8 -18],  $t=3.16$ ,  $z=2.99$ , FWE-SVC  $p=.013$ , Figure 2). Mean contrast estimates across the cluster were extracted to explore the pattern of the interaction. As can be seen from Figure 2, the interaction was driven by a significantly greater amygdala response to (fear/eyes>calm/eyes) than (fear/face>calm/face) in CP/CU- ( $t(16)=2.19$ ,  $p=.043$ ), and a significant difference in the opposite direction in TD Controls ( $t(16)=-2.22$ ,  $p=.041$ ). Comparing TD Control and CP/CU-groups directly, there was a significantly greater response to (fear/eyes>calm/eyes) in CP/CU- than in TD Controls

( $t(32)=2.21, p=.034$ ), and to (fear/face>calm/face) in TD Controls compared with CP/CU- ( $t(32)=2.09, p=.045$ ). The only significant simple effect was a greater response to fear/eyes relative to calm/eyes in CP/CU- ( $t(16)=2.51, p=.023$ ).

\*\*\*\*\*Figure 2\*\*\*\*\*

No other contrasts involving group were significant in the amygdala region of interest. Although not specifically hypothesised, we report two results from the whole brain analysis which survived cluster-level FWE-correction at the whole brain level after initial thresholding at  $p<.005, k>10$ . For the contrast CP/CU->TD Controls, a response was seen in a cluster encompassing subgenual anterior cingulate cortex and orbitofrontal cortex (sgACC/OFC) indicating a greater response to (fear/eyes>calm/eyes)>(fear/face>calm/face) in CP/CU- (peak=[4 30 -14],  $t=4.18, z=3.84, p<.001, k=1542$ ). The contrast CP/CU->CP/CU+ yielded one cluster surviving cluster-level FWE-correction in left middle temporal gyrus (peak=[-48 -14 -22],  $t=4.69, z=4.23, p=.019, k=570$ ). Post-hoc analyses showed these interactions were driven by crossover effects, as for the amygdala result above (see Figure 3 and the supplementary materials for further information).

\*\*\*\*\*Figure 3\*\*\*\*\*

*Relationships Between Behavioural and fMRI Data:* Both RT and fMRI data showed a disproportionate response to the fear/eyes condition in the CP/CU- group relative to both the other experimental conditions and the other groups (most consistently versus the TD Controls). We explored potential relationships between RTs and the amygdala effect hypothesised a priori by creating a single metric for each variable reflecting difference values for (fear/eyes>calm/eyes)>(fear/face>calm/face). A positive value on this metric indicates slower RTs/greater amygdala response to fear/eyes relative to other conditions.

Bivariate correlations between RT and amygdala response in each group showed a significant positive correlation in CP/CU- ( $r=.50, p=.043$ ), but no significant relationships in the other two groups

(for TD Controls,  $r=-.42$ ,  $p=.093$ ; for CP/CU+,  $r=-.038$ ,  $p=.88$ ). The correlation in CP/CU- could not be explained by co-morbid anxiety, depression, or ADHD symptoms: including these as covariates  $r=.58$ ,  $p=.030$ .

To test whether the relationship between RT and amygdala response was significantly stronger in CP/CU- than in the other groups, a custom univariate ANOVA was conducted with amygdala response as the dependent variable, mean-centred RT as a covariate and Group as a fixed factor. Modelled effects included the main effects of RT and Group, and the RT\*Group interaction term. There was no main effect of RT ( $p=.57$ ), a marginal main effect of Group ( $p=.070$ ), and a significant interaction between RT and Group ( $F(2,45)=3.74$ ,  $p=.031$ ). This suggested significant differences between groups in the slopes indexing the relationship between RT and amygdala response (Figure 4). Post hoc analyses showed that there was a significant difference between slopes for CP/CU- and TD Controls (RT\*Group interaction  $F(2,30)=7.59$ ,  $p=.010$ ), with this result surviving Bonferroni correction for multiple comparisons across the three groups. The difference between CP/CU- and CP/CU+ was marginal ( $p=.086$ ), and there was no difference between CP/CU+ and TD Controls ( $p=.35$ ).

\*\*\*\*\*Figure 4\*\*\*\*\*

## Discussion

The current study investigated behavioural and neural consequences of directing attention to the eye region of fearful vs. calm faces in children with conduct problems and differing levels of callous-unemotional traits. Contrary to our first hypothesis, amygdala response to fearful faces in children with conduct problems and high levels of CU traits (CP/CU+) did not increase when participants looked for a dot near the eye region of fearful faces compared with searching across the whole face. However, in line with our second hypothesis, children with conduct problems and low levels of CU traits (CP/CU-) showed increased left amygdala response to the fear/eyes condition relative to both other conditions and TD Controls. This was accompanied by increased reaction times, with the RT

increase specific to fearful eyes correlating with amygdala response in CP/CU- but not in TD Controls or CP/CU+. The CP/CU- group also showed increased neural responses to fearful eyes in the subgenual anterior cingulate/orbitofrontal cortex (sgACC/OFC) (relative to TD Controls), and left middle temporal gyrus (relative to CP/CU+).

It is important to consider why directing attention to the eye region during fear processing did not result in increased amygdala response in CP/CU+. One interpretation is that amygdala response in this group is largely immutable to the effects of manipulating attentional focus. Under this interpretation, improved fear recognition when focusing on the eye region (Dadds et al., 2006) would not be mediated by increased amygdala response. An alternative explanation relates to the nature of task demands. It has been suggested that fear processing deficits in CP/CU+ are associated with a reduced ability to reflexively shift attention to the salient eye region, a process that may be mediated by the basolateral amygdala (Gamer & Buchel, 2009; Moul et al., 2012). In the fear/eyes condition, attention was already focused on the eye region, meaning no amygdala-mediated reflexive shift was needed. Additionally, the instruction to look for a dot may have introduced unforeseen processing biases. For example, relative to free viewing conditions, the 'eyes' blocks may have increased focus on the eye region, while 'face' blocks may have decreased it. It is worth noting that the current study did not find a reduction across conditions in amygdala response to fear in CP/CU+, as has been reported under free viewing conditions (Marsh et al., 2008; Jones et al., 2009). Thus, it may be that the task was not optimal for detecting conditions under which a fear processing deficit might be elicited or ameliorated in CP/CU+.

Previous studies have shown a hyper-reactive affective profile in CP/CU- (Frick et al., 2003a; Dadds et al., 2006) and the current data suggest that reactivity to emotion may be augmented further when attention is directed to the eye region, which is high in affective salience (Adolphs et al., 2005). RT data further show that task performance in this group was specifically slowed during the fear/eyes condition. The significant positive relationship between RTs and amygdala reactivity in the CP/CU- group suggests that increased reactivity as indexed by amygdala response is associated with



a reduction in task performance. It is unlikely that these results are driven by anxiety levels, since TD and CP/CU- groups did not differ on this measure. It is also unlikely that the results can be explained by other symptoms on which the groups differed (i.e. ADHD and MDE), since the CP/CU+ group also showed elevated symptoms but did not differ from TD controls on either RT data or amygdala response. Instead, increased amygdala reactivity and slower RTs suggest that children with CP/CU- have difficulty implicitly or automatically regulating emotional responses in pursuit of a goal (Ochsner & Gross, 2005). This complements well-documented reports of difficulties with explicit emotion regulation in everyday life in this group (Frick & Morris, 2004). Indeed, difficulties with automatic emotion regulation may contribute to the development of expressed behaviours such as reactive aggression (Eisenberg et al., 2010).

These data are in line with a recent behavioural study exploring interactions between attention and affective processing in adults with externalizing behaviours (Baskin-Sommers et al., 2012). Using an instructed fear paradigm, this study found that externalizing behaviours were not associated with a global hyper-reactivity effect, but with increased emotional reactivity specifically when attention was focused on threat-related information. Interestingly, as in the current dataset, this study also found evidence for greater amygdala response in high-externalizing participants compared with low-externalizing participants when attention was focused on threat. Together, these data suggest the importance of understanding the specific conditions under which emotional hyper-reactivity is seen in externalizing conditions such as CP/CU-. This is necessary to elucidate neurocognitive mechanisms underpinning such behaviours, and may provide insights that will improve current approaches to intervention and prevention.

Although not predicted a priori, significantly increased neural responses to fearful eyes were seen in the CP/CU- group in sgACC/OFC (relative to TD Controls), and in the left middle temporal gyrus (relative to CP/CU+). The sgACC and medial OFC form part of an extended network involved in the experience and regulation of emotional states (Drevets et al., 2008). More specifically, the OFC and amygdala have been implicated in directing attention to affective stimuli (Zikopoulos & Barbas,

2012) and in the integration of emotion and cognitive control (Pessoa, 2008). Our data suggest aberrant cognitive control of emotion in CP/CU-, which may extend to sgACC/OFC function. Future studies should investigate further the role of these regions in reactive aggressive conduct problems. The difference between CP/CU- and CP/CU+ in the middle temporal gyrus is particularly difficult to interpret since this region is not typically activated during facial emotion processing, and indeed was not activated under any condition in the TD Control group (Figure 3b).

In summary, this is the first fMRI study to compare CP/CU-, CP/CU+ and TD Control children on an explicit facial emotion processing task. The use of a concurrent cognitive task introduced an implicit emotion regulation component. Children with CP/CU-, i.e. those most likely to display reactive aggression, showed increased amygdala reactivity compared with TD Controls, specifically in response to fearful eyes. This was correlated with longer RTs in the fear/eyes condition relative to control conditions. These data are in line with cognitive and behavioural profiles showing increased emotional reactivity in CP/CU-, and extend our knowledge to suggest specific conditions under which hyper-reactivity may be elicited in neural circuitry engaged in emotion-cognition interactions.

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## Tables and Figure Legends

### Tables

**Table 1:** Demographic data presented by Group. Numbers in parentheses show standard deviations.

### Figures

**Figure 1:** Mean RT differences plotted by Group and Condition. The significant Emotion\*Region interaction is driven by the CP/CU- group, who showed significantly slower RTs to fear/eyes than calm/eyes (the blue bar for CP/CU-). This group also showed significantly slower RTs for the interaction term (fear/eyes>calm/eyes)>(fear/face>calm/face) (the difference between the dark and pale bars) i.e. the fear/eyes condition had a disproportionate slowing effect on RTs in CP/CU-, but not in the other two groups.

**Figure 2:** Emotion\*Region\*Group interaction in the left amygdala (peak=[-18 -8 -18]), driven by a significantly greater response for (fear/eyes>calm/eyes)>(fear/face>calm/face) in CP/CU- relative to TD Controls. Top: Bars indicate mean contrast estimates across the cluster ( $k=6$ ) surviving FWE correction within a 3mm-radius bilateral sphere centred on central amygdala co-ordinates [ $\pm 20 -8 -16$ ]. The CP/CU+ group are shown for comparison, and do not differ significantly from either group. Bottom: Overlay shows the significant cluster overlaid on a mean T1 scan from all participants.

**Figure 3:** Regions showing an Emotion\*Region\*Group interaction at a whole brain cluster-corrected threshold of  $p<.05$ , FWE. Overlays are displayed at the initial threshold of  $p<.005$ ,  $k\geq 10$ . a) Significantly greater response in CP/CU- than in TD Controls in the subgenual ACC, extending into the OFC. b) Significantly greater response in CP/CU- than in CP/CU+ in the middle temporal gyrus.

**Figure 4:** Relationship between RT and amygdala response for the contrast (fear/eyes>calm/eyes)>(fear/face>calm/face), divided by Group. Slopes differed significantly between TD controls and CP/CU-, in which a significantly positive relationship between RT and amygdala response was seen.

**Figure 1**

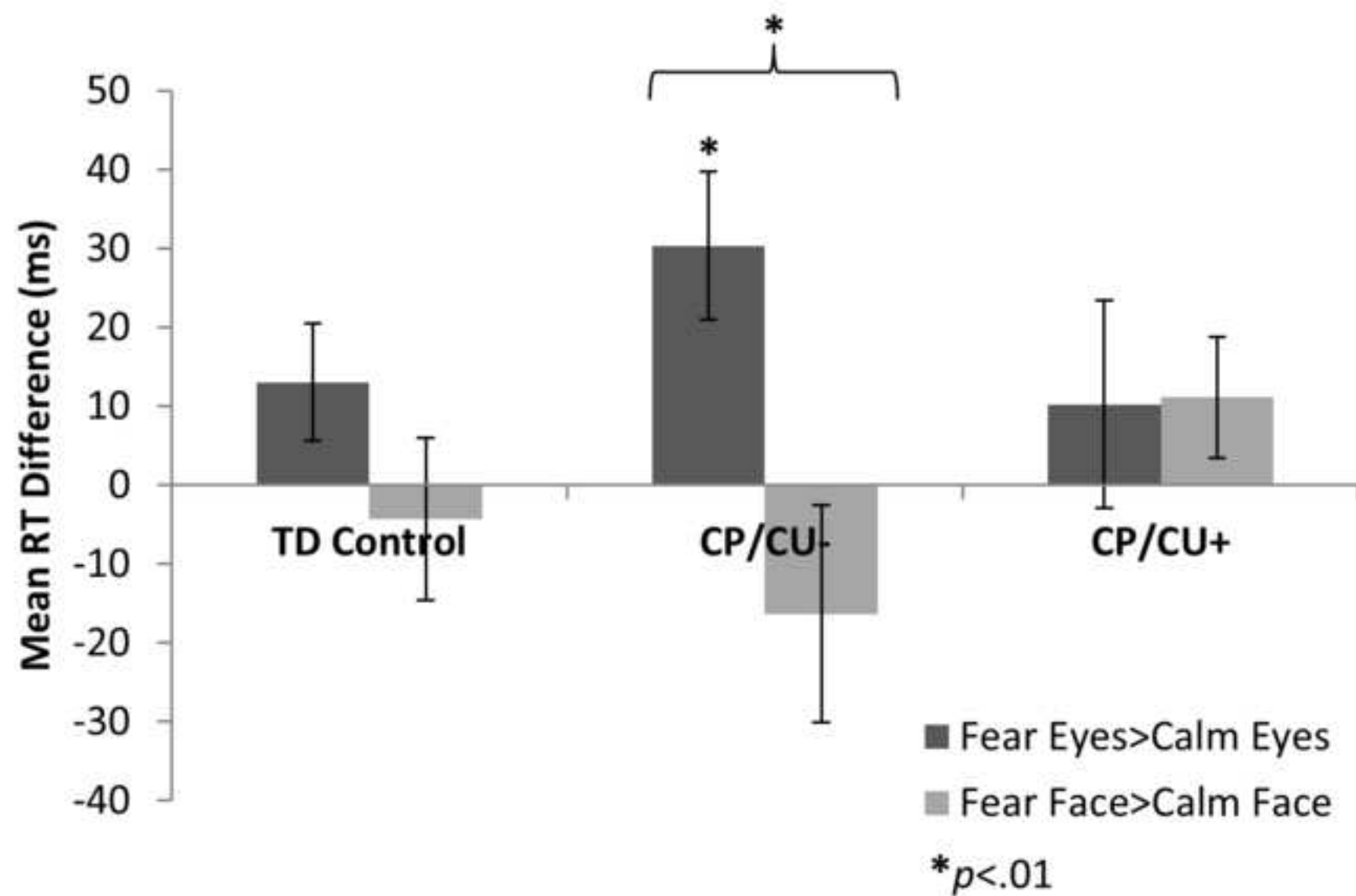




Figure 2

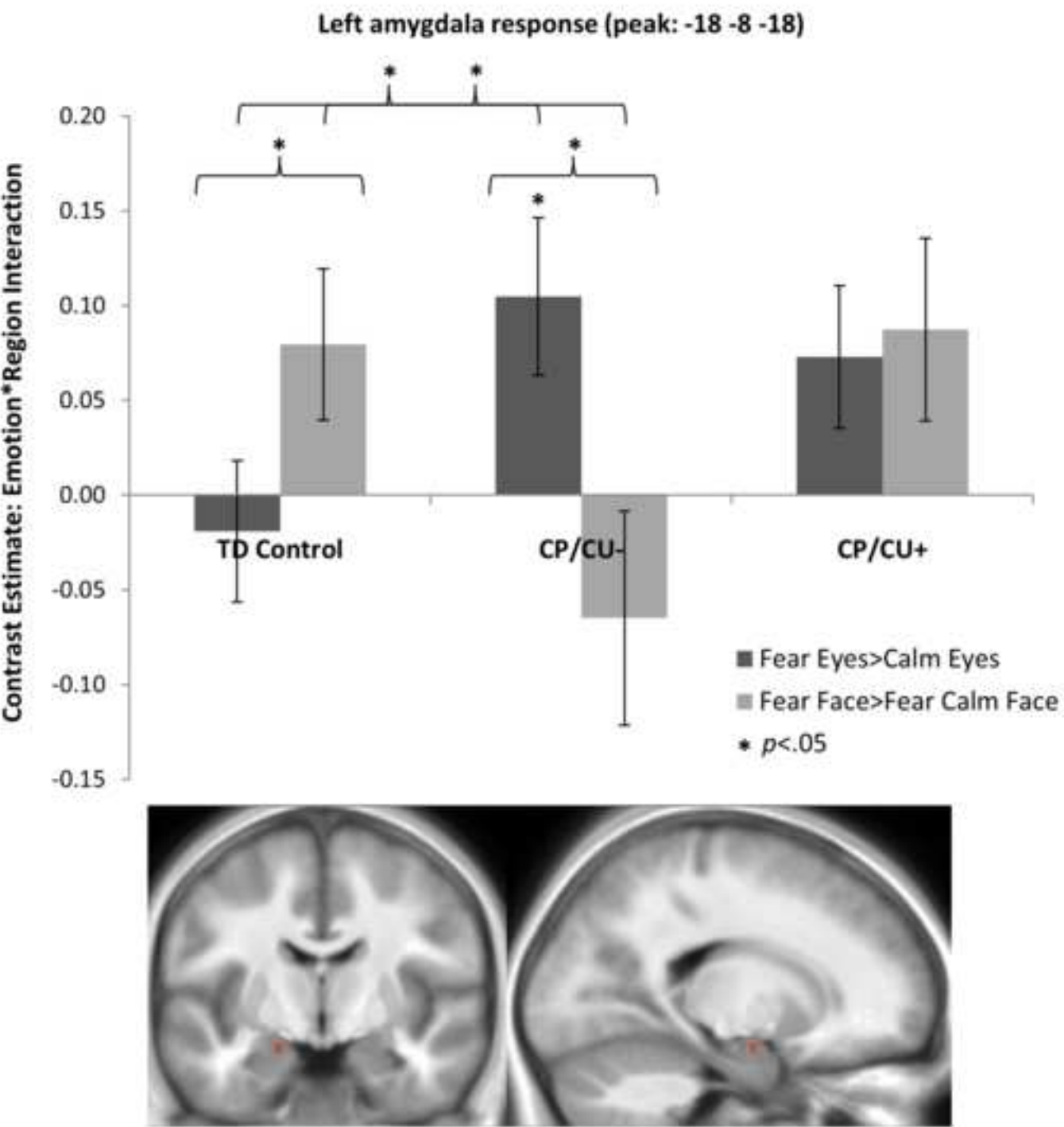
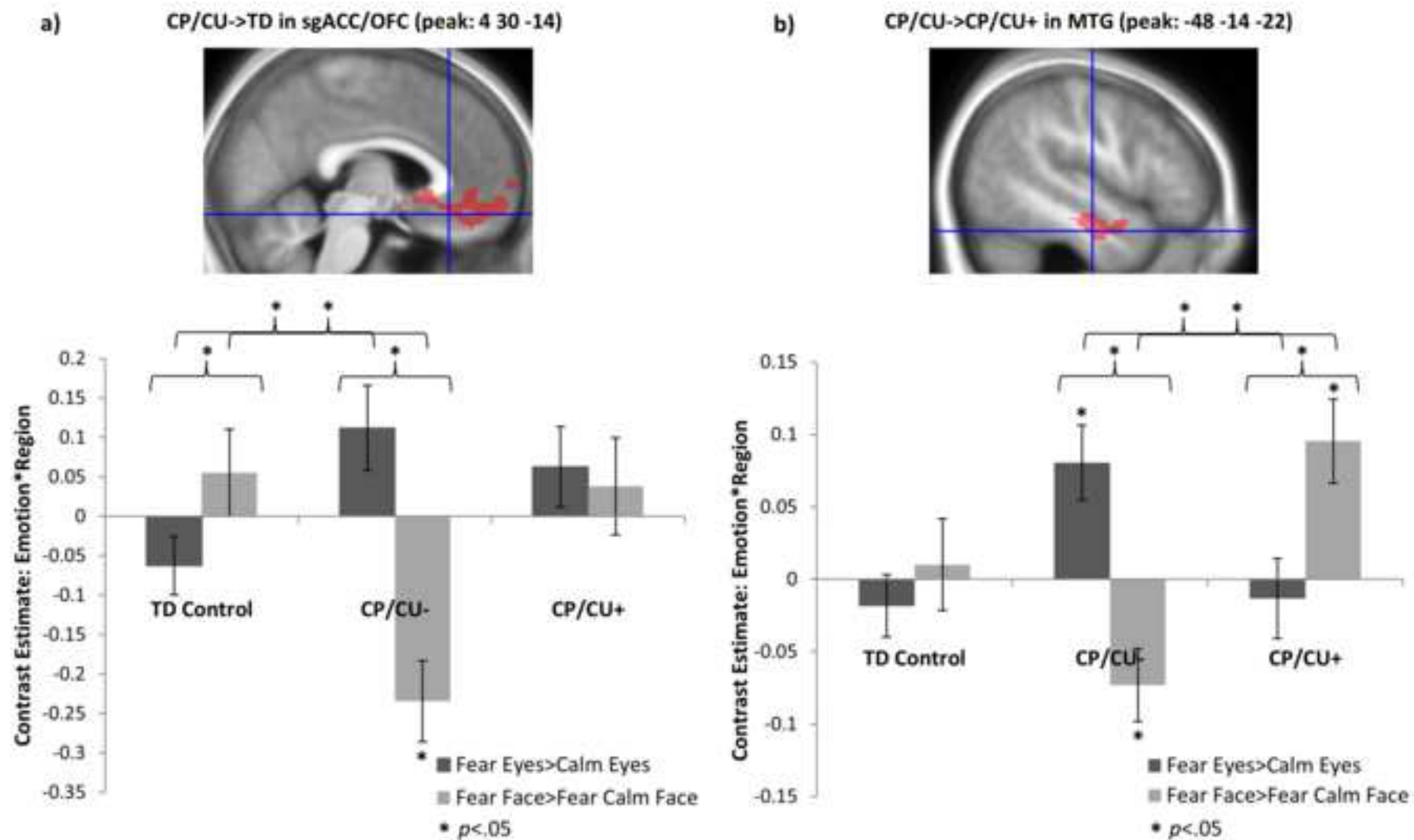


Figure 3  
[Click here to download high resolution image](#)

Figure 3



**Figure 4**

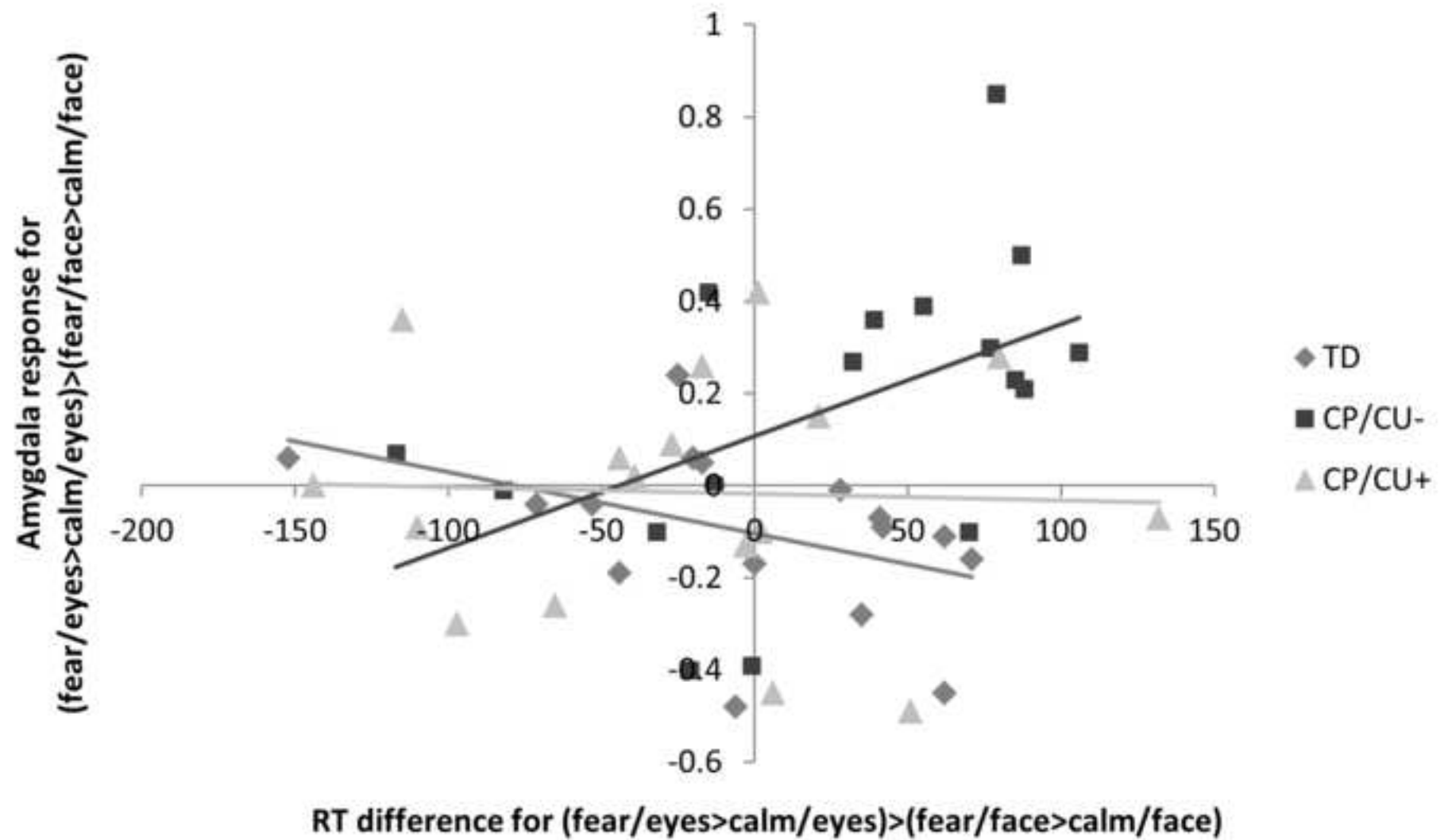


Table 1 - Demographic data. In all columns, numbers in parentheses show standard deviation.

	Group			P value	Post hoc*
	TD Controls <sup>1</sup>	CP/CU- <sup>2</sup>	CP/CU+ <sup>3</sup>		
Characteristics and questionnaires	(n=17)	(n=17)	(n=17)		
Age <sup>b</sup>	13.51 (1.60)	14.54 (1.58)	13.99 (1.94)	.227	
Socio-Economic Status <sup>b</sup>	2.73 (.83)	2.76 (1.24)	3.12 (1.08)	.496	
Full IQ score from 2-subtest WASI <sup>c</sup>	106.71 (12.27)	102.88 (11.51)	98.35 (11.64)	.130	
Ethnicity <sup>b,e</sup>	15:1:1	10:4:3	13:1:3	.357	
Handedness <sup>b,f</sup>	12:4:1	13:4:0	15:2:0	.675	
Inventory of Callous-Unemotional Traits <sup>d</sup>	24.00 (5.81)	35.35 (7.87)	53.35 (5.60)	<.001	1<2<3
Child and Adolescent Symptom Inventory					
Conduct Disorder <sup>d</sup>	.53 (.80)	8.14 (3.64)	13.36 (6.77)	<.001	1<2<3
Attention Deficit Hyperactivity Disorder <sup>g</sup>	9.71 (6.04)	21.84 (11.44)	30.29 (9.64)	<.001	1<2<3
Generalised Anxiety Disorder <sup>g</sup>	3.59 (3.16)	6.90 (4.42)	8.24 (5.02)	.008	1<3
Major Depressive Episode <sup>g,h</sup>	2.71 (1.93)	5.73 (3.41)	5.88 (3.61)	.006	1<2/3
Alcohol Use and Disorders <sup>c</sup>	1.18 (1.70)	4.00 (5.61)	4.47 (7.13)	.161	
Drug Use and Disorders <sup>c</sup>	.00 (.00)	2.47 (5.27)	1.00 (2.55)	.111	

\*  $p < .05$ , Bonferroni corrected

<sup>a</sup>All  $p$ -values obtained using  $t$ -tests except for Ethnicity and Handedness (Fisher's exact tests used)

<sup>b</sup>Measures taken at screening phase, parent report

<sup>c</sup>Child at scanning session

<sup>d</sup>Measures taken at screening phase, parent and teacher report

<sup>e</sup>White:Black:Mixed

<sup>f</sup>Right:Left:Ambidextrous

<sup>g</sup>Measures taken at scanning session - parent report

<sup>h</sup>Missing data from 1 participant with conduct problems

## **Supplementary Materials for ‘Neural responses to fearful eyes in children with conduct problems and varying levels of callous-unemotional traits’**

### **Supplementary Methods**

Males aged 10-16 were recruited from the community via newspaper advertisements and local schools. Screening questionnaires were administered to parents and teachers of 176 boys whose families expressed an interest in taking part and provided informed consent; and were scored by a trained research assistant according to standard published guidelines. These yielded: a research diagnosis of current conduct problems; dimensional assessment of CU traits; an overall psychopathology screen; demographic data for group matching purposes (socio-economic status, parent-defined ethnicity, and handedness); and information regarding previous neurological or psychiatric diagnoses. Current conduct problems were assessed using the Child and Adolescent Symptom Inventory (CASI-4R; Gadow & Sprafkin, 2009) Conduct Disorder subscale (CASI-CD), and CU traits were assessed using the Inventory of Callous-Unemotional Traits (ICU; Essau et al., 2006). Both were scored by taking the highest ratings from either the parent or the teacher questionnaire for any given item (Piacentini et al., 1992). The Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) was used as a brief screening measure for psychopathology in the typically developing (TD) control group.

On the basis of the screening information participants were invited for an fMRI scan. CASI-CD symptom severity scores were used to make the research diagnosis of current conduct problems. Symptom severity cut-off scores for inclusion in the conduct problems group were 3+ (ages 10-14) and 6+ (ages 15-16). Scores of this magnitude and above are associated with a clinical diagnosis of conduct disorder (ref), with an agreement between the screening cut-off scores for CASI-CD (completed by both parent and teacher) and clinical diagnoses of .95 (sensitivity) and .56 (specificity). There were no restrictions on ICU score for the conduct problems group. TD control participants were matched to conduct problems participants on verbal/performance IQ, age,

handedness, ethnicity and socio-economic status, but scored in the normal range for the CASI-CD and on each SDQ subscale. All control participants also scored below the conduct problems group median ( $=44.5$ ) on the ICU.

We obtained written informed consent from parents and written assent from participants. We scanned a total of 55 children (38 with conduct problems, 17 typically developing controls), yielding a final sample of usable data from 34 boys with conduct problems and 17 controls (exclusions as described in the main text). Assignment to CU group took place after these exclusions had been made on the basis of a median split on ICU scores, and yielded two groups: conduct problems with low CU traits (CP/CU-,  $N=17$ ) and conduct problems with high CU traits (CP/CU+,  $N=17$ ).

## **Supplementary Results**

### *fMRI Data: Emotion\*Region\*Group interaction: deconstructing interactions in non-predicted regions*

There was an effect of CP/CU->TD Controls for the contrast (fear/eyes>calm/eyes)>(fear/face>calm/face) in a cluster encompassing subgenual anterior cingulate cortex and orbitofrontal cortex (sgACC/OFC) (peak=[4 30 -14],  $t=4.18$ ,  $z=3.84$ ,  $p<.001$  FWE-corrected at the cluster level,  $k=1542$ ). As can be seen in Figure 3a, this effect was driven by a significantly greater response across the cluster to (fear/eyes>calm/eyes) than (fear/face>calm/face) in CP/CU- ( $t(16)=4.28$ ,  $p=.001$ ), and the reverse pattern in TD Controls ( $t(16)=-2.59$ ,  $p=.02$ ). Comparing groups, there was also a greater response to (fear/eyes>calm/eyes) in CP/CU- than TD controls ( $t(32)=2.66$ ,  $p=.012$ ), and a greater response to (fear/face>calm/face) in TD controls than in CP/CU- ( $t(32)=-3.84$ ,  $p=.001$ ). Looking at simple effects showed that the result was driven largely by CP/CU-, who showed a significantly larger response to calm/face than fear/face ( $t(16)=-4.55$ ,  $p<.001$ ), and a marginally greater response to fear/eyes than calm/eyes ( $t(16)=2.07$ ,  $p=.055$ ). Simple effects within the TD Control group were not significant.

There was also an effect of CP/CU-> CP/CU+ for the contrast (fear/eyes>calm/eyes)> (fear/face>calm/face) in left middle temporal gyrus (peak=[-48 -14 -22],  $t=4.69$ ,  $z=4.23$ ,  $p=.019$ ,  $k=570$ ). As can be seen from Figure 3b), this effect was driven by a significantly greater response across the cluster to (fear/eyes>calm/eyes) than (fear/face>calm/face) in CP/CU- ( $t(16)=3.59$ ,  $p=.002$ ), and the reverse pattern in CP/CU+ ( $t(16)=-3.47$ ,  $p=.003$ ). Comparing groups, there was also a greater response to (fear/eyes>calm/eyes) in CP/CU- than CP/CU+ ( $t(32)=2.48$ ,  $p=.019$ ), and a greater response to (fear/face>calm/face) in CP/CU+ than in CP/CU- ( $t(32)=-4.39$ ,  $p<.001$ ). Simple effects showed a significantly greater response to fear/eyes than calm/eyes in CP/CU-, but the reverse pattern for faces (calm/face>fear/face) ( $ps<.05$ ). In CP/CU+, there was a greater response to fear/face than calm/face ( $t(16)=3.30$ ,  $p<.005$ ), but no difference between fear/eyes and calm/eyes conditions.

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## Supplementary Tables

**Supplementary Table 1:** Regions showing a main effect across all groups for the contrasts Fear>Calm and Calm>Fear. Results are reported at a threshold of  $p<.005$ ,  $k>10$ . BA=Approximate Brodmann area in which the peak voxel is located. L/R=left/right, peak voxel=MNI co-ordinates, k=cluster size, ext.=extends into adjacent region.

Brain Region	BA	L/R	Peak Voxel	k	t	z
<b>Fear&gt;Calm (across Eyes/Face conditions)</b>						
Fusiform gyrus (ext. inferior occipital gyrus)	20, ext. 19	R	44 -36 -16	417	4.41	4.02
Superior temporal gyrus	22	R	50 -52 6	463	4.32	3.95
Temporal pole (ext. inferior frontal gyrus)	38, ext. 47	R	40 22 -28	167	4.23	3.88
Occipital gyrus	18	L	-30 -86 -20	288	3.95	3.66
Superior temporal gyrus	21	R	48 -26 -6	47	3.83	3.56
Fusiform gyrus (ext. parahippocampal gyrus)	37, ext. 19	L	-34 -38 -18	78	3.71	3.46
Superior frontal gyrus	10	R	8 64 28	29	3.16	3.00
Middle temporal gyrus	37	R	38 -60 0	29	3.06	2.91
Amygdala	-	L	-20 -8 -14	20	3.00	2.85
Middle frontal gyrus	46	R	58 30 22	24	2.99	2.85
Superior frontal gyrus	9	-	0 56 38	13	2.88	2.76
<b>Calm&gt;Fear</b>						
Superior frontal gyrus	10		24 44 20	128	4.02	3.71
Cingulate gyrus	24		-14 14 36	64	3.94	3.65
Caudate head (ext. bilaterally)	-		10 14 4	270	3.90	3.61
Anterior cingulate	24		-8 30 20	103	3.72	3.47
Thalamus	-		-20 -20 4	43	3.72	3.47
Cerebellum	-		10 -62 -26	25	3.11	2.95
Superior temporal gyrus	41		-46 -38 16	24	3.07	2.92
Superior frontal gyrus	8		18 28 42	14	2.92	2.79



**Supplementary Table 2:** Regions showing an Emotion\*Region interaction effect

(fear/eyes>calm/eyes)>(fear/face>calm/face) across groups. Results are reported at a threshold of  $p<.005$ ,  $k>10$ . BA=Approximate Brodmann area in which the peak voxel is located. L/R=left/right, peak voxel=MNI co-ordinates, k=cluster size, ext.=extends into adjacent region.

Brain Region	BA	L/R	Peak Voxel	k	t	z
<b>(Fear/Eyes&gt;Calm/Eyes)&gt;(Fear/Face&gt;Calm/Face)</b>						
Anterior cingulate	24	R	10 16 24	99	5.17	4.59
Posterior cingulate	30, ext. 29	L	-10 -54 12	345	4.88	4.38
Middle frontal gyrus (inc. white matter)	9	L	-26 18 26	361	4.34	3.97
Anterior cingulate (ext. medial frontal gyrus)	32, ext. 10	L	-14 34 2	598	4.26	3.90
Mid-cingulate gyrus	24	L	-10 -4 40	146	3.77	3.51
Precentral gyrus	6	L	-44 -18 28	110	3.69	3.44
Middle temporal gyrus	21	R	62 2 -26	31	3.68	3.43
Postcentral gyrus	43	L	-58 -12 18	107	3.45	3.24
Medial frontal gyrus	10	L	-14 50 -6	35	3.37	3.18
Caudate	-	R	14 14 10	29	3.29	3.11
Postcentral gyrus	2	R	58 -24 38	20	3.23	3.06
Thalamus	-	L	-14 -22 8	25	3.19	3.02
Thalamus	-	-	0 -6 12	46	3.13	2.98
Middle frontal gyrus	9	R	30 22 28	13	3.06	2.91
Medial frontal gyrus	10	R	14 54 6	32	3.05	2.90
Precentral gyrus	6	R	36 -12 36	22	3.03	2.88
Middle temporal gyrus	21	L	-62 0 -18	11	2.98	2.84
Lingual gyrus	19	L	-14 -64 -10	24	2.97	2.83
Superior temporal gyrus	22	L	-56 -6 -8	12	2.95	2.81
Superior temporal gyrus	41	R	48 -28 8	18	2.95	2.81
Superior frontal gyrus	8	R	18 16 46	10	2.88	2.75